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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,780	12/26/2000	Tanja Ouimet	P06910US00/BAS	3825

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STITES & HARBISON PLLC
1199 NORTH FAIRFAX STREET
SUITE 900
ALEXANDRIA, VA 22314

EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/647,780	OUIMET ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15 and 16* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,11,13,15 and 16* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 7-10 and 12 as well as 1-6, 11, 13 and 15-16 in part concerning SEQ ID NO:2.

The Amendment filed on Nov. 19, 2003 and Declaration under Rule 132 filed on Nov. 19, 2003 are acknowledged. The amendments to the claims have been entered as requested. Claims 1-13 and 15-16 are pending in the application. Claims 1-6, 11, 13 and 15-16, in part concerning SEQ ID NO: 4, are the subject of this Office Action. Claims 1-6, 11, 13 and 15-16 in part concerning SEQ ID NO: 2, as well as claims 7-10 and 12 are withdrawn from examiner's consideration as directed to the non-elected invention.

DETAILED ACTION

1. Objection

The objection to the specification for a vague definition of the term "biologically active", "similar" and "metalloprotease activity" is withdrawn, because the amended claims not recite the term.

Claim 3 is missing "group of" after the words "from the".

2. Rejections

2.1. 35 USC section 101

The amended claims 1-2 and depending claims 4-6, 11, 13, 15 and 16, are not anymore rejected under 35 U.S.C. 101 because the asserted specific utility is credible in the light of Declaration under Rule 132. The genus of isolated polypeptides comprising amino acid sequence encoded by SEQ ID NO:3 of the instant application encompasses,

as evidenced in the Declaration, a zincin enzyme having the same substrates and inhibitors as rat neprilysin of SEQ ID NO:2 of the instant application.

Rejection of claims 1-6, 11, 13, 15 and 16 under 35 USC § 112, the first paragraph is withdrawn because the claims have been amend.

2.2. 35 USC section 112, second paragraph

Rejection of claims 1–2, 4-6, 11, 13, 15 and 16 is withdrawn, because the indefinite phrase "a biologically active fragment of SEQ ID NO: 4" is not recited in the claims.

2.3. 35 USC section 112, first paragraph

3.3.1. Lack of written description

Claim 1, 6, 11, 13, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, for reasons stated in the previous Office Action and reiterated herein.

Claim 1, 6, 11, 13 and 15-16 are rejected as directed to polypeptide comprising an amino acid sequence encoded by the nucleic acid sequence SEQ ID NO: 3 and methods of use of said polypeptide.

The claims are directed to a large and variable genus of polypeptides. From the point of view of structure, the specification disclose only a single species of the claimed genus, i.e. the polypeptide of SEQ ID NO:4. However, the specification is silent about any structure/function relationship for a polypeptide comprising an amino acid sequence that is encoded by SEQ ID NO:3, and the function of SEQ ID NO:4 is as such not

disclosed. Thus, the structure of the claimed genus is insufficiently described, although, in the light of the Declaration under Rule 132 the function of the genus of the polypeptides is that of being a neprilysin. The Applicants have not provided information sufficient to put one of skill in the art in possession of the structural attributes and features of the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filled.

Claims 2, 4 and 5 are rejected under 35 U.S.C. 112, for the reasons stated in the previous Office Action and reiterated herein.

The claims are directed to the large and variable genus of DNA molecules that comprise a nucleotide sequence set forth by SEQ ID NO: 3, to vector and host cells transfected with said vector.

The claims are generic and lacking functional and structural description of claimed DNA molecules. The specification discloses only a single species of the claimed genus, i.e. SEQ ID NO: 3. However, this species is lacking a functional description because the amino acid sequence that is supposed to be encoded by SEQ ID NO: 3 is not taught by the disclosure. For that reason, the function of such a sequence and of SEQ ID NO:3 is unknown. The structure and function of the other species of the claimed genus are not disclosed. Applicants do not teach the structure of any DNA molecule comprising SEQ ID NO:3 and having the desirable function to encode a metalloprotease. The scope of claim 2 encompasses nucleotide sequences

that encode polypeptides that may or may not have a desirable function of metalloprotease.

Thus, because the disclosure does not provide information sufficient to put one of skill in the art in possession of the attributes and features of species within the claimed genus, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filled.

In addition, claims 15 and 16 are rejected for reasons stated in the previous Office Action and repeated bellow. Claim 15 recites "the peptide transmission in which NEP2 participates." The specification is silent as to in which peptide transmission a polypeptide comprising the amino acid sequence encoded by SEQ ID NO:3 is involved. Furthermore, with regards to claim 16 Applicants do not disclose any peptide transmission that is specifically related and/or disturbed in the group of diseases recited by the claim. Hence, because the disclosure does not provide information sufficient to put one of skill in the art in possession of the attributes and features of the peptide transmission in which the polypeptide comprising the amino acid sequence encoded by SEQ ID NO:3 is involved, one skilled in the art cannot reasonably conclude that the Applicant had possession of the claimed invention at the time the instant application was filled.

Traversing, in their Remarks, rejection of claims 15-16 made in the previous Office Action Applicants submit, "Example 4 in the present application

indicates that NEP2 is involved in the metabolism of neuronal and/or hormonal messenger peptides" (page 3, line 2).

Applicants' argument has been fully considered, but is found not persuasive. Example 4 provides information on expression of the NEP2 of rat, not claimed by Applicants in the examined set of claims. Applicants disclose that this NEP2 is "expressed in the heart, the liver, the digestive system and the brain" (page 13, line 13), and conclude, "These locations indicate the participation of NEPII in the proteolysis of hormones and of peptide neurotransmitters, or of their precursors, coming from or acting on theses diverse organs. It consequently becomes advantageous, for therapeutic puroposes, to affect the corresponding peptide transmissions by inhibiting NEP II" (page 14, line 1).

Even if the expression of the polypeptide comprising the sequence encoded by human sequence of SEQ ID NO:3 were the same, Applicants are in possession of "indication" and not an invention. Hormones, peptide neurotansmitters, and their precursors are large and versatile genera of proteins. Applicants have not disclosed any species of said genera as being affected by a polypeptide that comprises a sequence encoded by SEQ ID NO: 3. Since none of hormones, peptide neurotansmitters or their precursors are disclosed, the disclosure is also silent about any pathologies in which these hormones, neuropeptides or their precursors are involved.

3.3.2. Scope of enablement

Claims 1, 6, 11, 13, 15 and 16 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide identified by SEQ ID NO: 4, does not reasonably provide enablement for all peptides that comprise a polypeptide encoded by SEQ ID NO: 3.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The genus of polypeptides claimed is a large and variable genus lacking enabling description; see the above rejection for lack of written description.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses any polypeptide comprising a polypeptide encoded by the DNA molecule of SEQ ID NO: 3.

The source of this polypeptide may be man-made or any living organism. While methods of gene manipulation are well known in the relevant art, and skills of the

artisans highly developed, constructing the extremely large number of all possible DNA molecules encoding these polypeptides, subsequently expressing them, and checking enzymatic activity of expressed polypeptides is outside the realm of routine experimentation.

The disclosure does not provide characteristics of claimed invention. Applicants did not provide any guidance as to the structure of polypeptide comprising amino acid sequence encoded by SEQ ID NO: 3, i.e., a full size enzyme and its variants. For the same reasons the specification is missing any instructions as to how to construct a polypeptide having a neprilysin activity wherein amino acid sequence encoded by SEQ ID NO: 3 constitute the only known fragment of said polypeptide. Without further guidance on the part of Applicants as to the structure of the claimed polypeptide experimentation left to those skilled in the art is improperly extensive and undue.

Claims 2 and 4-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the DNA identified by SEQ ID NO: 3, does not reasonably provide enablement for all the DNA molecules that comprise SEQ ID NO: 3.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The genus of DNA molecules that comprise molecule of SEQ ID NO: 3 is a large and variable genus encompassing the species that do not encode the protein having the desired functionality.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses any isolated nucleic acid molecule that comprise SEQ ID NO: 3.

The source of this molecule is man-made or any living organism. While methods of isolating and structure manipulation of DNA molecules are well known in the relevant art, and skills of the artisans highly developed, isolating or constructing an extremely large number of all possible DNA molecules characterized under a)-c) is outside the realm of routine experimentation.

The disclosure does not provide sufficient identifying characteristics of the claimed genus of DNA molecules. Applicants did not provide any guidance or examples as to what a DNA molecule comprising SEQ ID NO: 3 should be, how to construct it so that it had the capacity of encoding the polypeptide with required functionality. Without guidance as to the structure and function of the claimed genus of DNA molecules the experimentation left to those skilled in the art is improperly extensive and undue.

3.4. 35 USC, 102

Claim 6 remains rejected under 35 U.S.C. 102(b) for the reasons stated in the previous Office Action, paper No 16 and reiterated herein. Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Shipp et al. (Molecular cloning of the common acute lymphoblastic leukemia antigen (CALLA) identifies type II integral membrane protein, Proc. Natl. Acad. Sci. USA, 1988, 85, 4819-4823, and Ritz et al. (A monoclonal antibody to human acute lymphoblastic leukaemia antigen, Nature 1980, 283, 583-585.

The amended claim 6 is directed to mono-or polyclonal isolated antibodies or their fragments, chimeric isolated antibodies or immunoconjugates, characterized in that they are obtained using a polypeptide and are capable of recognizing specifically a polypeptide comprising the amino acid sequence encoded by SEQ ID NO: 3.

Shipp et al., page 4821, Fig. 2, teach a protein called CALLA antigen containing in positions 583-696 the amino acid sequence identical in 66.7% to amino acid residues 1-114 of SEQ ID NO: 4 (SEQ ID NO: 4 comprises the polypeptide encoded by SEQ ID NO: 3 in positions 1-109). Ritz et al. teach production of monoclonal antibody against CALLA. Ritz et al teach the invention of claim 6, because the antibody specific to the sequence that is 66.7% identical to SEQ ID NO: 4 will combine to SEQ ID NO: 4 or any polypeptide containing amino acid sequence encoded by SEQ ID NO: 3. Those skilled in the art realize that an antibody "cross-reacts", i.e. binds to more than one protein sequence, which means that specifically recognize more than one protein. For example, Bost et al. (Antibodies against a Peptide Sequence within the HIV Envelope Protein Crossreact with Human Interleukin-2, Immunological Investigations, (1988, 17,

pages 577-586; see the attached copy) have shown that one kind of antibodies reacts with two different proteins, because of the presence in their sequences of homologous fragments, consisting of **4-6 identical amino acid residues.** Such short sequences of amino acids consist what is called antibody's epitope. As evidenced in the alignment of CALLA and SEQ ID NO: 4 of the instant application sent to the Applicants previously, CALLA and SEQ ID NO: 4, or for that matter a sequence encoded by SEQ ID NO: 3, have more than one fragment consisting of more than 10 identical amino acids.

In their "REMARKS" Applicants write, "the rejection of claim 6 is now moot since claim 6 no longer encompasses antibodies directed against polypeptides homologous to SEQ ID NO: 4. Accordingly, claim 6 is not anticipated by Ritz et al. since Ritz et al. teach production of an antibody against a sequence which is 66.7% identical to SEQ ID NO: 4." (page 4, line 3).

This argument of Applicants has been fully considered, but is found not persuasive. Applicants claim antibodies to polypeptides comprising a sequence encoded by SEQ ID NO: 3. SEQ ID NO: 4 comprises in positions 1-109 the amino acid sequence encoded by SEQ ID NO: 3. An antibody specific to the polypeptide comprising sequence that is 66.7% identical to SEQ ID NO: 4 will combine to the polypeptide comprising to SEQ ID NO: 4 or the sequence encoded by SEQ ID NO: 3 because that sequence comprises the first 109 amino acids of SEQ ID NO: 4. As evidenced in the alignment of CALLA and SEQ ID NO: 4 of the instant application sent to the Applicants previously, CALLA and SEQ ID NO: 4, or for that matter a sequence

encoded by SEQ ID NO: 3, have more than one fragments consisting of more 10 identical amino acids.

Since the Office does not have a laboratory to test the reference by Ritz et al., it is Applicant's burden to show that the reference antibodies do not bind to a polypeptide comprising the amino acid sequence encoded by SEQ ID NO: 3 as recited in the claim. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

4. Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Patent Examiner
Art Unit 1652

REBECCA E. PRUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600